NIH OBA Incident Report

For reporting Human Gene Transfer Adverse Events a separate template is available at:
http://www4.od.nih.gov/oba/RAC/Adverse_Event_Template.doc

Does this incident involve research subject to the *NIH Guidelines*?	Yes If no, this incident does not have to be reported to OBA
Institution name:	University of Iowa
Date of report:	February 17, 2012
Reporter name and position:	Louis Kirchhoff, MD, MPH; IBC Chair
Reporter telephone:	319-356-7227
Reporter email:	louis-kirchhoff@uiowa.edu
Date of incident:	1/17/2012
Name of principal investigator:	Alexander R. Horswill, PhD
Is this an NIH funded project?	No
If yes, please provide:	NIH grant or contract number: N/A
	NIH funding institute or center: N/A
	NIH program officer contact information (name, email etc): N/A
What was the **nature** of incident?	Possible personnel exposure to a recombinant strain of *Staphylococcus aureus*

Did the Institutional Biosafety Committee (IBC) approve this research	Yes
If yes, please provide:	Approval date: 9/29/2011
	Approved biosafety level for the research: BSL2
	Additional approval requirements: None
What section(s) of the *NIH Guidelines* is the research subject to?	III-D-1
Has a report of this incident been made to other federal or local agencies? If so please indicate by checking the appropriate box.	No

DESCRIPTION OF INCIDENT: (continued)

Introduction:
On January 18, 2012, the University of Iowa's Biosafety Officer (BSO) became aware that an incident resulting in injury of a graduate student the previous day involved a recombinant strain of *S. aureus*. That injury is described in the First Report of Injury form. This incident constitutes a violation of the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (Appendix G-II-B-2-k) and therefore must be reported to the Office of Biotechnology Activities at the National Institutes of Health (NIH/OBA). This report, which follows our initial notification of NIH/OBA on January 18, 2012, provides a description of the investigation of this incident, an analysis of the factors underlying the incident, and the University's planned remedial measures intended to prevent the occurrence of incidents of this type in the future.

Description of incident:
This incident involved a graduate student in the laboratory of Dr. Alexander Horswill, a principal investigator in the Department of Microbiology who has an approved rDNA Registration Document that covers work with recombinant *S. aureus*. The student was working with a recombinant *S. aureus* which carries a targeted mutation in a regulator gene. As the student removed the cap from a glass test tube containing the bacteria, the tube broke and cut his finger. The student reported to the University Employee Health Clinic and was sent to the Emergency Room where he received two stitches and tetanus vaccination. He also given a prescription for a three-day course of trimethoprim/sulfamethoxasole. On the day following the incident the BSO met with the student and the principal investigator to obtain additional information regarding the incident. Importantly, the principal investigator explained that although possible, it was highly unlikely that there would have been any *S. aureus* on the neck of the glass tube that broke and cut the student's finger. The student took the antibiotic as prescribed. No local evidence of infection developed at the site of the cut and subsequently it has healed completely.

As of the time of the incident, the student had completed all online training required by the University, which includes Basic Biological Safety; Lab Chemical Safety; PPE Awareness for Labs; and rDNA Research, *NIH Guidelines*.

Laboratory issues uncovered by the investigation:

- At the time the incident occurred the student was not wearing any PPE. It was emphasized during the meeting that disposal gloves and a laboratory coat are required for BSL2 work with hazardous agents.
- Glass tubes are used for frozen storage of the *S. aureus* strains used in the project. The principal investigator stated that they use glass tubes instead of plastic simply because his Department supplies them free of charge.

Has the IBC reviewed this incident?	Yes If yes, please provide a copy the minutes of the IBC meeting in which the incident was reviewed.
Has a root cause for this incident	Yes

been identified?	If yes please describe: The use of glass tubes to store frozen *S. aureus* strains.
Describe measures taken by the institution to mitigate any problems identified. For measures identified but not yet taken, please include a timeline for their implementation: (use additional space as necessary) • The student assured the BSO that the required PPE will be worn while he works with hazardous materials in the laboratory. • At the request of the IBC, the principal investigator will encourage a culture of safety in his laboratory by emphasizing that laboratory coats and appropriate disposable gloves must be worn when working with hazardous materials, and then will ensure that such PPE is always worn when required. • The principal investigator will look into the possible use of plastic instead of glass tubes and report to the BSO within one month.	

- **Please provide copies of any documents referenced in this report.**
- **Additional information may be requested by OBA after review of this report depending on the nature of the incident.**

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Does this incident involve research subject to the *NIH Guidelines*?	Yes If no, this incident does not have to be reported to OBA
Institution name:	University of Iowa
Date of report:	5/30/2012
Reporter name and position:	Louis V. Kirchhoff, MD, MPH; IBC Chair
Reporter telephone:	319-356-7227
Reporter email:	louis-kirchhoff@uiowa.edu
Date of incident:	5/1/2012
Name of principal investigator:	Jeffery L. Meier, MD
Is this an NIH funded project?	Yes
If yes, please provide:	NIH grant or contract number: 5T32AI007533-12
	NIH funding institute or center: NIAID
	NIH program officer contact information (name, email etc): Ed McSweegan, phone: 301-402-8370, mcsweegan@nih.gov
What was the **nature** of incident?	Possible personnel exposure to a recombinant strain of human CMV (rhCMV)

Did the Institutional Biosafety Committee (IBC) approve this research	Yes
If yes, please provide:	Approval date: 11/24/2009
	Approved biosafety level for the research: BSL2
	Additional approval requirements: None
What section(s) of the *NIH Guidelines* is the research subject to?	III-D-2
Has a report of this incident been made to other federal or local agencies? If so please indicate by checking the appropriate box.	Other: Iowa City Department of Veterans Affairs Medical Center Oversight Committee

DESCRIPTION OF INCIDENT: (continued)

Introduction:
On May 2, 2012, the University of Iowa's Biosafety Officer (BSO) became aware that an incident resulting in injury of a graduate student the previous day involved a recombinant strain of human cytomegalovirus (rhCMV). This incident constitutes a violation of the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (Appendix G-II-B-2-k) and therefore must be reported to the Office of Biotechnology Activities at the National Institutes of Health (NIH/OBA). This report, which follows our initial notification to NIH/OBA on May 2, 2012, provides a description of the investigation of this incident, an analysis of the factors underlying the incident, and the University's planned remedial measures intended to prevent the occurrence of incidents of this type in the future.

Description of incident:
This incident involved a graduate student in the laboratory of Dr. Jeffery Meier, a principal investigator with appointments in the Department of Internal Medicine, University of Iowa, and at the Iowa City Department of Veterans Affairs Medical Center. The student was working with an attenuated recombinant strain of human cytomegalovirus (rhCMV; Towne vaccine strain) that carries an origin of replication for a bacterial artificial chromosome, a gene that encodes a green fluorescent protein, and genes that confer resistance to chloramphenicol and kanamycin. This rhCMV strain is not known to cause disease in humans and has been used in human vaccine trials in the past. Moreover, there is no evidence from the vaccine trials that the Towne strain can establish latent infection in persons exposed to it. The student was working in a biological safety cabinet and was infecting mammalian cells in culture with the rhCMV. As the student disposed of a glass pipette into a sharps container, another pipette used just previously in her work was sticking out of the container, penetrated the glove she was wearing, stuck her finger, and resulted in a superficial puncture evidenced by a dot of blood at the site. The student squeezed additional blood from the site, washed the area two times with soap and water and rinsed it with 70% ethanol.

Subsequent to the incident, the student contacted the principal investigator, filed a First Report of Injury form, and reported to the University Employee Health Clinic (UEHC). Blood was drawn at UEHC for pregnancy testing (negative), anti-CMV IgM (negative), and anti-CMV IgG (positive).

Three days after the incident was reported, the BSO met with the student and the principal investigator to obtain additional information regarding the incident. There was no deviation from the laboratory's SOP for working with rhCMV. The student was wearing gloves and a lab coat and the biological safety cabinet in which she had been working was certified. Occupational health requirements for personnel working with this virus restrict pregnant women from working with high titer hCMV.

As of the time of the incident, the student had completed all online training required by the University, which includes Basic Biological Safety; Lab Chemical Safety; Bloodborne Pathogens for Labs, PPE Awareness for Labs; and rDNA Research, *NIH Guidelines*. The student had completed additional training in the Veterans Administration system that included Biological Safety, Lab Chemical Safety and Bloodborne Pathogen training.

The student did not develop any signs or symptoms of infection subsequent to the incident, and thus there is no indication that she has

become infected with the rhCMV strain with which she was working. The fact that she had anti-CMV IgG shortly after the incident is indicative of prior infection.

Laboratory issues uncovered by the investigation:

- At the time the incident occurred, the sharps container was over-filled and a pipette sticking out of the container punctured her finger.

Has the IBC reviewed this incident?	Yes If yes, please provide a copy the minutes of the IBC meeting in which the incident was reviewed.
Has a root cause for this incident been identified?	Yes If yes please describe: The over-filled sharps container.

Describe measures taken by the institution to mitigate any problems identified. For measures identified but not yet taken, please include a timeline for their implementation: (use additional space as necessary)

- The student was cautioned not to fill the sharps containers above the fill line. Basic Biological Safety and Bloodborne Pathogen training courses instruct laboratory staff to replace sharps containers when they become 2/3 full, and the student was instructed to follow this directive.
- The principal investigator was encouraged to switch from glass to plastic pipettes for all work in his laboratory involving hazardous materials. Links to the web pages of several vendors that market sterile plastic pipettes that are appropriate for cell culture work of the type performed in the principal investigator's laboratory were given to him.

- **Please provide copies of any documents referenced in this report.**
- **Additional information may be requested by OBA after review of this report depending on the nature of the incident.**

NIH OBA Incident Reporting Template

For reporting Human Gene Transfer Adverse Events a separate template is available at:
http://www4.od.nih.gov/oba/RAC/Adverse_Event_Template.doc

Does this incident involve research subject to the *NIH Guidelines*?	YES If no, this incident does not have to be reported to OBA
Institution name:	University of Iowa
Date of report:	March 1, 2013
Reporter name and position:	Louis Kirchhoff, MD, MPH; IBC Chair
Reporter telephone:	319-356-7227
Reporter email:	louis-kirchhoff@uiowa.edu
Date of incident:	Identified February 1, 2013
Name of principal investigator:	Kathleen A. Sluka, PT, PhD
Is this an NIH funded project?	Yes
If yes, please provide:	NIH grant or contract number: RO1 AR061371
	NIH funding institute or center: NIAMS
	NIH program officer contact information: William P. Tonkins; 301-594-5032; william.tonkins@nih.hhs.gov
What was the **nature** of incident?	Other - please describe: Mice injected with recombinant herpes simplex virus-1(rHSV-1) were housed at animal biosafety level 1 (ABSL1) rather than at ABSL2, as approved by the IBC

Did the Institutional Biosafety Committee (IBC) approve this research	YES If yes, on what date? Most current rDNA protocol was approved on 8/5/2010
If yes, please provide:	Approval date: 8/5/2010
	Approved animal biosafety level for the research: ABSL2
	Additional approval requirements: None
What section(s) of the *NIH Guidelines* is the research subject to?	III-D-1
Has a report of this incident been made to other federal or local agencies? If so please indicate by checking the appropriate box.	No

DESCRIPTION OF INCIDENT:

Introduction:
On February 1, 2013, the University of Iowa's Biosafety Officer (BSO) became aware that a principal investigator (PI) was housing mice injected with rHSV-1 in ABSL1, despite the fact that the work had been approved by the IBC at ABSL2. This incident constitutes a violation of the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (Appendix G-II-B-2-k) and therefore must be reported to the Office of Biotechnology Activities at the National Institutes of Health (NIH/OBA). This report provides a description of the investigation of this incident, an analysis of the factors underlying the incident, and the University's planned remedial measures intended to prevent the occurrence of incidents of this type in the future.

Description of incident:
This incident involved the laboratory of Dr. Kathleen Sluka, PI in the Department of Physical Therapy, who has an approved rDNA Registration Document that covers work with rHSV-1 in mice. Dr. Sluka has had IBC approval for this project since 2004 and the work has consistently been approved at ABSL2. Most recently, in July 2012, Dr. Sluka submitted a request for an amendment to the approved rDNA registration document and the work was again assigned ABSL2 containment. Despite this consistent record of ABSL2 approval from the IBC, Dr. Sluka's laboratory staff has always housed the mice injected with rHSV-1 at ABSL1. This non-compliance was identified during a routine visit by a post-approval monitor from the office of the Institutional Animal Care and Use Committee (IACUC).

Shortly after being made aware of this non-compliance, the BSO held a meeting with the IACUC Director, the Clinical Veterinarian from the Office of Animal Resources (OAR) and Dr. Sluka. Dr. Sluka stated that many years ago a staff member from OAR or the Environmental Health & Safety Office (EHS) had stated to her that ABSL1 housing was appropriate for the mice injected with rHSV-1. Dr. Sluka could not provide any documentation of this discussion, however, and could not recall the name of the staff member who made the latter statement. Moreover, all submitted rDNA Registration Documents as well as the recent amendment submitted by Dr. Sluka and approved by the IBC from 2004 to the present have specified that ABSL2 containment was required for the mice injected with rHSV-1.

At the meeting Dr. Sluka agreed to immediately stop her experiments involving rHSV-1 and mice.

As of the time of the non-compliance was discovered, laboratory staff listed on Dr. Sluka's rDNA Registration Document had completed all online training required by the University, which includes Basic Biological Safety; Lab Chemical Safety; PPE Awareness for Labs; and rDNA Research- *NIH Guidelines*. Dr. Sluka had completed rDNA Research- *NIH Guidelines*

training.

Has the IBC reviewed this incident?	YES If yes, please provide copies of the minutes of the IBC meetings in which the incident was reviewed. February 14 and 28, 2013
Has a root cause for this incident been identified?	YES If yes please describe: Dr. Sluka stated that she assigned responsibility for administration and implementation of her rDNA Registration Documents and the related amendment to a member of her laboratory staff and did not read the documents before she signed them and submitted them to the IBC.

Describe measures taken by the institution to mitigate any problems identified. For measures identified but not yet taken, please include a timeline for their implementation: (use additional space as necessary)

For many years the IBC has had a process in place for registering proposed work involving rDNA in which only a PI can sign and submit to the IBC a completed rDNA Registration Document, which includes an attestation regarding compliance with the framework for the research approved by the IBC. Similarly, a request for an amendment to an approved rDNA Registration Document can only be submitted to the IBC by a PI. This process only breaks down, as in the case at hand, if the PI does not properly supervise subordinate personnel in the administration and implementation of the rDNA Registration Documents. To reduce the likelihood in the future of incidents similar to that described herein, the importance of carefully supervising subordinate personnel who deal with the administration and implementation of regulatory processes as well as the need for detailed review of regulatory documents before signing and submitting them will be reiterated with Dr. Sluka. Moreover, a brief reminder along these lines will be inserted in the next issue of *LabNews*, which is published by EHS staff and circulated throughout the research community at the University.

Finally, the University's Animal Protocol currently is undergoing extensive revision. One of the goals of the revision is to ensure that the ABSL listed on the Animal Protocol is the same as that approved by the IBC. To that end the revised Animal Protocol will include a question that asks PIs whose proposed work involves rDNA to indicate what ABSL was approved by the IBC, and if it is not ABSL1 the PI will be required to complete a containment form. Administrative reviewers of the rDNA Registration Document will then check the PI's Animal Protocol to verify that the ABSL approved by the IBC has been entered.

NIH OBA Incident Reporting Template

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http://www4.od.nih.gov/oba/RAC/Adverse_Event_Template.doc

Does this incident involve research subject to the *NIH Guidelines*?	YES If no, this incident does not have to be reported to OBA
Institution name:	University of Iowa
Date of report:	May 2, 2013
Reporter name and position:	Louis V. Kirchhoff, MD, MPH; IBC Chair
Reporter telephone:	319-356-7227
Reporter email:	louis-kirchhoff@uiowa.edu
Date of incident:	Identified April 5, 2013
Name of principal investigator:	Wendy Maury, PhD
Is this an NIH funded project?	YES
If yes, please provide:	NIH grant or contract number: AI 077519
	NIH funding institute or center: NIAID
	NIH program officer contact information: Pat Repik, prepik@niaid.nih.gov
What was the **nature** of incident?	Other - please describe: Mice injected with recombinant vesicular stomatitis virus (VSV) pseudovirions were housed at animal biosafety level 1 (ABSL1) rather than at ABSL2, as approved by the IBC

Did the Institutional Biosafety Committee (IBC) approve this research	YES If yes, on what date? The most recent rDNA Registration document was approved on 3/29/2012
If yes, please provide:	Approval date: 3/29/2012
	Approved animal biosafety level for the research: ABSL2
	Additional approval requirements: None
What section(s) of the *NIH Guidelines* is the research subject to?	III-D-1
Has a report of this incident been made to other federal or local agencies? If so please indicate by checking the appropriate box.	No

DESCRIPTION OF INCIDENT:

Introduction:
On April 5, 2013, the University of Iowa's Biosafety Officer (BSO) became aware that a principal investigator (PI) had housed mice injected with VSV pseudovirions at ABSL1, despite the fact that the work had been approved by the IBC at ABSL2. This incident constitutes a violation of the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (Appendix G-II-B-2-k) and therefore must be reported to the Office of Biotechnology Activities at the National Institutes of Health (NIH/OBA). This report provides a description of the investigation of this incident, an analysis of the factors underlying the incident, and the University's planned remedial measures intended to prevent the occurrence of incidents of this type in the future.

Description of incident:
This incident involved the laboratory of Dr. Wendy Maury, a PI in the Department of Microbiology, who has an approved rDNA Registration document that covers work with VSV pseudovirions in mice. Dr. Maury's animal work with VSV pesudovirions was approved at ABSL2. After injection of the mice with the rDNA, however, they were housed at ABSL1. This non-compliance was identified through an email communication with the office of the Institutional Animal Care and Use Committee (IACUC).

Shortly after being made aware of this non-compliance, the BSO held a meeting with Dr. Maury. Dr. Maury stated that no experiments involving VSV pseudovirions in animals are being done currently. She further stated that when such experiments are resumed the animals will be housed at the approved containment of ABSL2.

At the time the non-compliance was discovered, laboratory staff listed on Dr. Maury's rDNA Registration Document had completed all online training required by the University, which includes Basic Biological Safety; Lab Chemical Safety; PPE Awareness for Labs; and rDNA Research- *NIH Guidelines*. Dr. Maury had completed the rDNA Research- *NIH Guidelines* training as required.

Has the IBC reviewed this incident?	YES If yes, please provide copies of the minutes of the IBC meetings in which the incident was reviewed. April 11 and 25, 2013
Has a root cause for this incident been identified?	YES If yes please describe: Dr. Maury assumed that the rDNA containment assignment for the VSV pseudovirions would be ABSL1 as it is for replication defective recombinant lentiviral systems. With this mindset, Dr. Maury did not take note that the rDNA Registration Document indicated that the work with recombinant VSV virions should be at ABSL2.

Describe measures taken by the institution to mitigate any problems identified. For measures identified but not yet taken, please include a timeline for their implementation: (use additional space as necessary)

The University's Animal Protocol currently is undergoing extensive revision. One of the goals of the revision is to ensure that the ABSL listed on the Animal Protocol is the same as that approved by the IBC. To that end the revised Animal Protocol will include a question that asks PIs whose proposed work involves rDNA to indicate the ABSL approved by the IBC, and if it is not ABSL1 the PI will be required to complete a containment form. Administrative reviewers of the rDNA Registration Document will then check the PI's Animal Protocol to verify that the ABSL approved by the IBC has been entered. We expect that the consistency between the rDNA Registration Document and the Animal Protocol will eliminate ambiguity as to what containment level is required for the proposed research.

- **Please provide copies of any documents referenced in this report.**
- **Additional information may be requested by OBA after review of this report depending on the nature of the incident.**

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Does this incident involve research subject to the *NIH Guidelines*?	YES If no, this incident does not have to be reported to OBA
Institution name:	The University of Iowa
Date of report:	May 31, 2013
Reporter name and position:	Louis V. Kirchhoff, MD, MPH; IBC Chair
Reporter telephone:	319-356-7227
Reporter email:	louis-kirchhoff@uiowa.edu
Date of incident:	April 18th, 2013
Name of principal investigator:	Stanley Perlman, MD, PhD
Is this an NIH funded project?	YES
If yes, please provide:	NIH grant or contract number: AI060699-07
	NIH funding institute or center: NIH NIAID
	NIH program officer contact information (name, email etc): Dr. Rachelle Salomon Influenza, SARS, & Related Viral Respiratory Diseases Section Respiratory Diseases Branch Division of Microbiology and Infectious Diseases NIAID/NIH/DHHS Room 3213 6610 Rockledge Dr. Bethesda, MD 20817 Phone: 301-402-2202 Fax: 301-496-8030 Email: salomonra@niaid.nih.gov
What was the **nature** of incident?	Personnel exposure Spill

Did the Institutional Biosafety Committee (IBC) approve this research	YES If yes, on what date? 5/26/2011
If yes, please provide:	Approval date: 5/26/2011
	Approved biosafety level for the research: BSL3
	Additional approval requirements: None
What section(s) of the *NIH Guidelines* is the research subject to?	Section III-D-1
Has a report of this incident been made to other federal or local agencies? If so please indicate by checking the appropriate box.	CDC

DESCRIPTION OF INCIDENT:

At 1:00 PM on April 18, 2013, an incident occurred in the autoclave room of a UI BSL3 laboratory that involved animal bedding from mice infected with wild-type and recombinant strains of SARS-CoV (Risk Group 3 organism). A laboratorian was loading the autoclave with animal cages containing bedding from infected animals. Cages were stacked on top of one another inside an autoclave bag which was loosely tied at the neck. As the bag was loaded into the autoclave, the top cage tilted sideways and tore a portion of the bag. Bedding spilled out of the cage, and a small amount spilled through the tear and onto the floor in front of the autoclave. The spill was not noticed by the laboratorian because the bedding fell behind bags of waste that were waiting to be autoclaved. The laboratorian then closed the autoclave door, started autoclave cycle, removed his PPE, and exited the facility according to protocol.

At 9:30 AM the following morning, the Associate Director of the BSL3 laboratory entered the autoclave room to load the remaining bagged waste into the autoclave. After loading and closing the door, she noticed the spilled bedding on the floor, which covered a circular area approximately 15 cm in diameter. She then gently sprayed the bedding with 10% bleach, covered it with 2 cloth diaper pads soaked in 10% bleach, and allowed it to soak for more than 30 minutes. During this period the Associate Director notified the ARO about the incident. Three other users of the BSL3 laboratory assisted in the clean-up. During entry the users donned standard PPE: scrubs, wrap-around gown, PAPR, double pair of gloves with initial pair taped to cuff of gown, as well as dedicated shoes, socks, and shoe covers. The walls, floor and ceiling of the autoclave room where the bedding was spilled were wiped down with 10% bleach, followed by a wipe-down with Spor-Klenz to remove the bleach film. The floor of the entire BSL3 facility was also wiped down with 10% bleach. All clean-up material was disposed of as biohazardous waste per protocol and was autoclaved prior to removal from the BSL3 laboratory.

Following the cleanup, an incident evaluation and risk assessment were performed by the ARO/ABSO, the Associate Director, and the laboratorian. The risk assessment determined that there was no potential exposure, as supported by the following evidence:

- The laboratorian was wearing the following PPE: scrubs, PAPR, double gloves with the initial gloves taped over the cuff of the gown, facility-dedicated shoes, socks and shoe covers. The Associate Director was wearing: scrubs, wrap-around gown, PAPR, double gloves with the initial gloves taped over the cuff of the gown, as well as facility-dedicated shoes, socks and shoe covers.
- All PPE that was worn was in good condition. PPE is inspected by each user upon donning and doffing to confirm that there are no tears and it was determined that the PAPR was intact and functioning properly.
- The autoclave is located inside the BSL3 laboratory and thus is under negative airflow.
- Although this spill was not immediately noticed, other laboratorians who entered the BSL3 facility between the time of the spill and the clean-up the following morning, including those who entered the autoclave room, were all wearing proper PPE, including a PAPR. The laboratorians who entered the BSL3 laboratory subsequent to the spill but before it was noticed by the Associate Director did not enter until nearly 2 hours after the spill had occurred, during which time several room air exchanges occurred (The times of the entries of other laboratorians were established by review of video surveillance).
- Because the PAPR was functioning properly it was determined that there was no potential exposure to the individual; therefore, no medical surveillance after the incident was required. It merits mention that all persons who work in the BSL3 laboratory are fully aware that they should report any signs or symptoms of illness any time they occur.

During this evaluation it was noted that proper reporting procedures were followed (ARO and PI) as well as proper clean-up of the spill once it was

discovered. One action item that resulted from this evaluation was that the laboratorian needed to be re-trained on proper loading of the autoclave, which includes use of the autoclave cart. Since this incident occurred, all BSL3 users were reminded to use the autoclave cart and autoclave discard pans on a daily basis for removal from the BSL3 laboratory, and they also were instructed on the proper bagging of cages to prevent them from toppling over and tearing the autoclave bag. Mock incidents are routinely conducted with all users of the BSL3 laboratory during annual refresher training. It should be noted that a mock hands-on drill to simulate a spill outside of primary containment was conducted in 2011 and reviewed during refresher training in 2012. After the incident described herein the laboratorian was instructed as to what he should have done and will be further retrained as part of the annual refresher training that is required for all BSL3-registered persons.

At the time of the incident the laboratorian was performing experiments classified as III-D-1 that were described in a rDNA Registration Document approved by the IBC on 5/26/2011. The recombinant SARS-CoV strains had E, C1 or F2 gene deletions. This spill was not reported to NIH/OBA per the reporting requirements outlined in Appendix G-II-C-2-q, again, since a determination was made that there was no potential for exposure. Presently, reporting spills to the IBC is not standard procedure. However we will make this part of our reporting process. As previously stated, it is our understanding that an overt exposure would be an incident that involves direct contact of an organism to the mucus membrane of an individual or a needle-stick. A potential exposure would be an incident that involves a spill outside of the BSC, if people working in the room were not using a functioning PAPR or other respiratory protection. The incident described herein was reported to CDC as a release only, because the evidence from the internal evaluation of the incident and risk assessment did not support the view that the incident was either an overt or potential exposure.

Has the IBC reviewed this incident?	YES If yes, please provide a copy the minutes of the IBC meeting in which the incident was reviewed.
Has a root cause for this incident been identified?	YES If yes please describe: The autoclave bag that contained the animal cages was not secured properly and the autoclave cart was not used for loading the waste into the autoclave.

Describe measures taken by the institution to mitigate any problems identified. For measures identified but not yet taken, please include a timeline for their implementation: (use additional space as necessary)

All BSL3 users have been reminded to use the autoclave cart and autoclave discard pans on a daily basis for processing and removal of biohazardous materials from the BSL3 laboratory. Users were also instructed on the proper bagging of cages to prevent them from toppling over and tearing the autoclave bag.

In addition, as a result of the CDC's Select Agent Program response to our Form 3 report of a release of agent, our BSL3 manuals will be revised to state that any release will be viewed as a potential exposure and subsequent medical evaluation and required reporting will be carried out. Within the next two months the relevant procedure manuals will be revised to reflect these procedural changes and then will be sent to the appropriate committees for review and approval.

- **Please provide copies of any documents referenced in this report.**
- **Additional information may be requested by OBA after review of this report depending on the nature of the incident.**

NIH OBA Incident Reporting Template

For reporting Human Gene Transfer Adverse Events a separate template is available at:
http://www4.od.nih.gov/oba/RAC/Adverse_Event_Template.doc

Does this incident involve research subject to the *NIH Guidelines*?	YES If no, this incident does not have to be reported to OBA
Institution name:	The University of Iowa
Date of report:	May 31, 2013
Reporter name and position:	Louis V. Kirchhoff, MD, MPH; IBC Chair
Reporter telephone:	319-356-7227
Reporter email:	louis-kirchhoff@uiowa.edu
Date of incident:	April 10, 2013
Name of principal investigator:	Bradley Jones, PhD
Is this an NIH funded project?	YES
If yes, please provide:	NIH grant or contract number: 2PO1AI044642 534 and 2U54AI057160
	NIH funding institute or center: NIH NIAID
	NIH program officer contact information (name, email etc): Michael Schaefer, MSchaefer@niaid.nih.gov
What was the **nature** of incident?	Personnel exposure Spill

Did the Institutional Biosafety Committee (IBC) approve this research	YES If yes, on what date? 8/4/2011
If yes, please provide:	Approval date: 8/4/2011
	Approved biosafety level for the research: BSL3
	Additional approval requirements: None
What section(s) of the *NIH Guidelines* is the research subject to?	III-D-1
Has a report of this incident been made to other federal or local agencies? If so please indicate by checking the appropriate box.	CDC

DESCRIPTION OF INCIDENT:

On April 10, 2013, an incident occurred in a University of Iowa BSL3 laboratory that involved a recombinant strain of *Francisella tularensis*, Schu S4 (Risk Group 3 organism). A laboratorian was removing supernatant from a 24-well plate which contained cells that had been infected with the bacteria 16 hours prior to the incident. While preparing to remove supernatant from the final well (approximately 1 ml), the plate slipped out of his hands and hit the diaper that covered the work surface inside the BSC; supernatant spilled out of the well onto the diaper and also onto the uncovered BSC surface. While no drops were observed to have fallen onto the laboratorian's gloved hands or gown, approximately 3 drops of the media dropped onto the lower part of the PAPR bib that he was wearing. As previously instructed, the laboratorian sprayed his gloved hands with disinfectant prior to removing them from the BSC. He then used a bleach wipe to wipe down his PAPR followed by spraying the PAPR hood with Sporklenz and waiting 30 minutes. During the 30 minute wait, the laboratorian contained and treated the spill inside the BSC by covering the area with CiDecon-soaked paper towels. The 24-well plate was disposed of as biohazard waste. The laboratorian removed his exterior PPE, exited the BSL3 laboratory, and reported the spill to the Associate Director, the RO, and the PI, as per protocol.

After an additional 30 minute wait, the Associate Director entered the BSL3 laboratory with the laboratorian to finish cleaning up the spill. Entry included donning standard PPE: scrubs, wrap-around gown, PAPR, double pair of gloves with initial pair taped to cuff of gown, dedicated shoes, socks and shoe covers. Following protocol, the spill was cleaned up in the following manner: the paper towels covering the spill were disposed of in biohazardous waste and the entire interior of the BSC and its contents, including the grill after removal, were sprayed down with 10% bleach, allowed to sit for 30 minutes, and then wiped down with 70% ethanol. As a precaution, the floor outside of the cabinet, the front of the BSC, and the support mechanism were also sprayed with 10% bleach followed by wipe down with 70% ethanol. All clean-up material was disposed of as biohazardous waste that ultimately was autoclaved prior to removal from the BSL3 laboratory.

After the spill was cleaned up, an incident evaluation and risk assessment were performed by the RO/BSO, ARO/ABSO, Associate Director, and the laboratorian. The risk assessment determined there was no potential exposure, as supported by the following evidence:

- The laboratorian was wearing all required PPE: scrubs, wrap-around outer gown, PAPR, and double gloves with the initial gloves taped over the cuff of the gown, in addition to facility-dedicated shoes, socks, and shoe covers.
- All PPE that was worn was in good condition; PPE is inspected by each laboratorian upon donning and doffing to confirm that there are no rips or tears and it was determined that the PAPR was intact and functioning properly.
- A majority of the liquid from the spill was contained in the biosafety cabinet, with only 3 drops found on the lower part of the PAPR bib.
- Because the PAPR was functioning properly it was determined that there was no potential exposure to the individual; therefore, no medical surveillance after the incident was required. It merits mention that all persons who work in the BSL3 laboratory are fully aware that they should report any signs or symptoms of illness any time they occur.

During this evaluation it was noted that proper reporting procedures were followed (RO, Associate Director, and PI) as well as proper clean-up of the spill. Mock incidents are routinely conducted with all users of the BSL3 laboratory during annual refresher training; a mock hands-on drill to simulate a spill outside of primary containment was conducted in 2011 and reviewed during refresher training in 2012. The laboratorian was immediately instructed again as to what he should have done and will be re-trained as part of the annual refresher training required for all registered individuals.

The laboratorian was working under a protocol that had been approved by the University of Iowa's IBC and is classified as III-D-1. This work is funded by NIH grants: 2PO1AI044642 534 and 2U54 AI057160, Project 14, awarded to the PI. The recombinant bacterial strain was designed by disrupting the function of FTT_1236 by inserting non-coding DNA; no antibiotic resistance markers were used. This release was not reported to NIH/OBA per the reporting requirements as outlined in Appendix G-II-C-2-q, again, as a determination had been made that there was no potential for exposure. At this time, reporting spills to the IBC is not standard procedure; however this will be made part of the reporting process. It is our understanding that an overt exposure would be an incident that involves direct contact of an organism to the mucus membrane of an laboratorian or a needle-stick; a potential exposure could be an incident that involves a spill outside of the BSC, if people working in the room did not employ the use of a functioning PAPR or respiratory protection. The incident described herein was reported to CDC as a release only, because the evidence from the internal evaluation of the incident and risk assessment did not support the view that the incident was either an overt or potential exposure.

Has the IBC reviewed this incident?	YES If yes, please provide a copy the minutes of the IBC meeting in which the incident was reviewed.
Has a root cause for this incident been identified?	YES If yes please describe: Gloved hands are routinely sprayed with disinfectant while working in the biosafety cabinet. The laboratorian's gloves were wet while he was handling the plate which caused it to slip out of his hands.

Describe measures taken by the institution to mitigate any problems identified. For measures identified but not yet taken, please include a timeline for their implementation: (use additional space as necessary)

All users will avoid handling cultures or plates while gloved hands are wet with disinfectant.

In addition, as a result of the CDC's Select Agent Program response to our Form 3 report of a release of agent, our BSL3 manuals will be revised to state that any release will be viewed as a potential exposure and subsequent medical evaluation and required reporting will be carried out. Within the next two months the relevant procedure manuals will be revised to reflect these procedural changes and then will be sent to the appropriate committees for review and approval.

- **Please provide copies of any documents referenced in this report.**
- **Additional information may be requested by OBA after review of this report depending on the nature of the incident.**

NIH OBA Incident Reporting Template

For reporting Human Gene Transfer Adverse Events a separate template is available at:
http://www4.od.nih.gov/oba/RAC/Adverse_Event_Template.doc

Does this incident involve research subject to the *NIH Guidelines*?	YES If no, this incident does not have to be reported to OBA
Institution name:	The University of Iowa
Date of report:	6/22/2013
Reporter name and position:	Louis V. Kirchhoff, MD, MPH; IBC Chair
Reporter telephone:	319-356-7227
Reporter email:	louis-kirchhoff@uiowa.edu
Date of incident:	6/4/2013
Name of principal investigators:	Drs. Paul McCray and Stanley Perlman
Is this an NIH funded project?	YES
If yes, please provide:	NIH grant or contract number: 5P01AI060699-07
	NIH funding institute or center: NIAID
	NIH program officer contact information (name, email etc): Dr. Rachelle Salomon Influenza, SARS, & Related Viral Respiratory Diseases Section Respiratory Diseases Branch Division of Microbiology and Infectious Diseases NIAID/NIH/DHHS Room 3213 6610 Rockledge Dr. Bethesda, MD 20817 Phone: 301-402-2202 Fax: 301-496-8030 Email: salomonra@niaid.nih.gov
What was the **nature** of incident?	Other - please describe: Biosafety cabinet (BSC) manual error resulted in possible exposure to potentially contaminated HEPA filter during motor replacement.

Did the Institutional Biosafety Committee (IBC) approve this research	YES If yes, on what date? 5/26/2011 (Perlman)
If yes, please provide:	Approval date: 5/26/2011 (Perlman); Work with non-recombinant SARS-CoV MA15 attenuated strain was approved by the Carver College of Medicine BSL3 Oversight Committee (McCray)
	Approved biosafety level for the research: BSL3
	Additional approval requirements: none
What section(s) of the *NIH Guidelines* is the research subject to?	III-D-1
Has a report of this incident been made to other federal or local agencies? If so please indicate by checking the appropriate box.	CDC State/Local Public Health

Please provide a narrative of the incident including a timeline of events. The incident should be described in sufficient detail to allow for an understanding of the nature and consequences of the incident. **Include the following information as applicable.**

INFORMATION ON FACILITY, AGENT, AND THOSE INVOLVED IN THE INCIDENT:

This incident occurred in a BSL3 facility that is comprised of several procedure rooms in which experiments involving viral Risk Group 3 organisms are performed. The Class II B2 biosafety cabinet (BSC)(The Baker Company, Sanford, Maine) involved in the incident is located in a procedure room used by research assistants who work for Drs. Paul McCray and Stanley Perlman. Experiments involving wild type and recombinant strains of SARS-CoV (Perlman) and the non-recombinant MA15 attenuated strain of SARS-CoV (McCray) are performed in the BSC. The MA15 strain of SARS-CoV is a mouse-adapted attenuated strain that was generated by serial passage of SARS-CoV Urbani strain in mice. Servicing of the BSCs at the University of Iowa is done under a contract with an outside company that provides NSF-certified technicians for the work (ENV Services, San Antonio, Texas). The contractor is responsible for training its technicians and relies on information provided by the manufacturers of the BSCs to develop standard protocols for certifications, repairs, etc. The contractor sent a technician to service the BSC in the BSL3 facility. The technician underwent required visitor training prior to entering the BSL3 facility, was escorted by the Associate Director, and was servicing the BSC when the incident occurred.

DESCRIPTION OF INCIDENT:

Although experiments with the above-mentioned strains of SARS-CoV had been performed in the BSC for approximately eight years, no experiments of this type had been done in it since 5/11/2013. The blower supply motor stopped working on 5/28/2013 and replacement was scheduled for 6/4/2013. While it is standard University of Iowa protocol to decontaminate BSCs prior to accessing potentially contaminated areas in the interior housing, the BSC technician stated that such decontamination is not required prior to servicing a Class II B2 BSC because the motor is self-contained and is adjacent to the air supply plenum, both of which are sealed off from potentially contaminated areas.

The Associate Director escorted the technician to the BSL3 facility on 6/4/2013 where they donned standard PPE prior to entry. Standard PPE includes: PAPR, disposable scrubs, wrap-around gown, two pairs of gloves with the initial pair taped to the cuff of the gown, dedicated shoes and socks, and shoe covers. The technician did not perform vaporized hydrogen peroxide decontamination prior to beginning the service because as noted it was his view that it was not needed for a Class II B2 BSC. Once he removed the access panel of the BSC to start the repair, it was clear that in this BSC the air supply plenum

and motor housing are not segregated from the potentially contaminated side of the exhaust filter and plenum. Thus his removal of the access panel of the BSC resulted in the possible exposure of the procedure room and the two persons in it to potentially contaminated areas inside the BSC. However, the building's HVAC system maintains a negative air pressure, which in each procedure room exhausts continuously through the BSC's exhaust filter. Once the two persons present realized the exhaust filter was exposed and the motor could not be removed in a self-contained fashion, Spor-Klenz was used to spray down all exposed parts of the BSC interior housing. The motor and casing were removed and placed on the floor on top of diaper pads/chucks. The motor was removed from its case and autoclaved prior to removal from the facility. The new motor was placed into the casing that had been wiped down with Spor-Klenz and then placed back into the BSC housing, which had also been wiped down with Spor-Klenz. After the new motor was tested to confirm it was operational, the access panel was put back in place. During this repair process, both the Associate Director and technician removed their outer gloves and replaced them in case there were tears or loss of integrity. When the two persons left the procedure room they each removed their outer pair of gloves, tape, and gown and placed them into a biohazard waste container. The technician followed proper PPE doffing procedure for exiting and temporarily left the BSL3 facility.

After escorting the technician out of the facility, the Associate Director returned to the procedure room and wiped down the outside of the BSC, the floor, chair and wall nearest the BSC with Spor-Klenz. After doing this the Associate Director notified the Alternate Responsible Official that vaporized hydrogen peroxide decontamination had not been done prior to removal of the BSC access panel and the discovery of exposed exhaust filter upon removal of the access panel during the repair.

The technician then was escorted back into the facility, donning standard PPE, in order to certify the cabinet. During the certification the technician's tools were placed on a diaper pad/chuck and wiped down with Spor-Klenz before removal. Once the certification was complete, the technician doffed his PPE and was escorted out of the BSL3 facility by the Associate Director. The Associate Director wiped down the hallway of the BSL3 suite with 10% bleach prior to doffing PPE and exited. All waste generated during this incident was placed in biohazard waste containers for autoclaving prior to removal from the BSL3 facility.

To gain more information regarding the interior design of this Class II B2 BSC, the Alternate Responsible Official spoke with technical managers at the company that manufactured the BSC and also with technical managers at the company contracted to service the BSCs. The managers at both companies indicated that Class II B2 BSC decontamination prior to motor replacement on a Class II B2 is not standard procedure. However, in further discussion it became clear that what the technician saw after removal of the access panel as well as the procedure to remove the motor itself was inconsistent with what is shown in manual provided with this Class II B2 BSC. The manufacturer has agreed to revise the manual based on this

experience and the service company will make it a standard procedure on our campus to perform vaporized hydrogen peroxide decontamination prior to removal of the access panel of any model of BSC in order to access the motor housing.

Throughout this incident standard PPE was worn (including a PAPR) by the two persons involved and the facility's HVAC system was fully functioning and under negative pressure. Thus there was very little potential for exposure. However, because the repair exposed the potentially contaminated exhaust filter, this is being reported as a potential exposure. The Alternate Responsible Official reviewed the signs and symptoms of SARS with the Associate Director and the technician on 6/5/2013, and reminded them to report any symptoms of illness. This action was determined by the Alternate Responsible Official, in consultation with the University Employee Health Clinic physician.

The Alternate Responsible Official alerted users of the [redacted] BSL3 facility to not enter this procedure room until it had been surface decontaminated. Surface decontamination of the room was accomplished using 10% bleach on 6/6/2013. All waste generated during the surface decontamination was placed in biohazardous waste containers and was autoclaved prior to removal from the BSL3 facility.

Has the IBC reviewed this incident?	YES If yes, please provide a copy the minutes of the IBC meeting in which the incident was reviewed.
Has a root cause for this incident been identified?	YES If yes please describe: Access to the motor housing was not as outlined in the manufacturer's manual.
Describe measures taken by the institution to mitigate any problems identified. For measures identified but not yet taken, please include a timeline for their implementation: (use additional space as necessary) As noted, the manufacturer of the BSC as well as the company contracted to service BSCs at the University were contacted regarding this occurrence. The manufacturer will revise the manual for this BSC model, since access to the motor is not accurately described in the manual. The company that services the BSCs will make it standard protocol to decontaminate all BSCs at the University prior to removal of an access panel and exposure of any interior housing of a BSC.	

- **Please provide copies of any documents referenced in this report.**
- **Additional information may be requested by OBA after review of this report depending on the nature of the incident.**

NIH OBA Incident Reporting Template

For reporting Human Gene Transfer Adverse Events a separate template is available at: http://oba.od.nih.gov/oba/rac/Adverse_Event_Template.pdf

Does this incident involve research subject to the *NIH Guidelines*?	YES
Institution name:	University of Iowa
Date of report:	November 2, 2013
Reporter name and position:	Louis Kirchhoff, MD, MPH; IBC Chair
Reporter telephone:	319-356-7227
Reporter email:	louis-kirchhoff@uiowa.edu
Reporter mailing address:	UIHC – SW54 GH Dept of Internal Medicine Iowa City, IA 52242
Date of incident:	October 4, 2013
Name of principal investigator:	Budd Tucker, Ph.D.
Is this an NIH funded project?	YES
If yes, please provide:	NIH grant or contract number: 1DP2OD007483
	NIH funding institute or center: NIH Director's Award
	NIH program officer contact information (name, email etc): Rochelle Galbraith, rochelle-galbraith@uiowa.edu
What was the **nature** of incident?	Personnel exposure Failure to obtain IBC approval

Did the Institutional Biosafety Committee (IBC) approve this research	The use of the viral vector and cell lines was approved by the IBC on 10/14/2010; however, subsequent injection of transfected cells into the pig animal model was not approved.
If yes, please provide:	Approval date: 10/14/2010
	Approved biosafety level(s) for the research: BSL2
	Additional approval requirements: None
What section(s) of the *NIH Guidelines* is the research subject to?	III-D-1
Has a report of this incident been made to other federal or local agencies? If so please indicate by checking the appropriate box.	No
Description of recombinant or synthetic agent or material involved (please indicate strain, attenuation etc. as relevant.)	Replication defective lentivirus expressing green fluorescent protein (GFP). The vector was purchased from Addgene and is an FIV backbone and contains a CMV promotor. This lentivirus was gag/pol deleted. Mouse cells were transduced with the recombinant lentivirus vector bearing the GFP gene and then injected into the pig via sub-retinal administration.

Please provide a narrative of the incident including a timeline of events. The incident should be described in sufficient detail to allow for an understanding of the nature and consequences of the incident. **Include the following information as applicable.**

DESCRIPTION OF INCIDENT: (use additional space as necessary)

Introduction:
On October 4, 2013, the University of Iowa's Biosafety Officer (BSO) became aware of a puncture wound incident resulting in injury of a research assistant. On October 10, 2013 it was determined that the syringe may have contained mouse cells transduced with a replication defective lentivirus expressing GFP. In addition, following discussion with the Principal Investigator (PI), it was determined that IBC approval had not been obtained for administration of these recombinant cells into pigs. This incident constitutes a violation of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (Appendix G-II-B-2-k) and therefore must be reported to the Office of Biotechnology Activities at the National Institutes of Health (NIH/OBA). This report, which follows our initial notification of NIH/OBA on October 10, 2013, provides a description of the investigation of this incident, an analysis of the factors underlying the incident, and the University's planned remedial measures intended to prevent the recurrence of incidents of this type.

Description of incident:
This incident involved a research assistant in the laboratory of Dr. Budd Tucker, a PI in the Department of Ophthalmology who has an approved rDNA Registration Document that covers work with replication defective vectors and cell lines. The assistant, along with two surgeons, was administering a recombinant mouse cell line which had been transfected with a lentiviral vector expressing GFP into a pig via sub-retinal injection. The experiment was a blind study such that the assistant was unaware which syringe held the recombinant cells or control saline. PPE worn at the time of administration included a gown, gloves and mask.

Following injection of the cells or saline, the syringe with cannula attachment was placed on a table for the duration of the surgery. During clean-up of the area, the assistant received a puncture to her right index finger. The assistant contacted a physician at the University Employee Health Clinic and discussed the incident. The physician instructed the assistant to monitor her health for symptoms suggestive of a viral infection, including fever or enlarged lymph nodes.

On the day after being informed about the incident the BSO met with the assistant and the PI to obtain additional information. Importantly, the PI explained that he had decoded the experiment and determined that the assistant had received a puncture wound from the control syringe containing saline. At that time no local or systemic evidence of infection was present.

As of the time of the incident, the assistant had completed all online training required by the University for general lab work, which includes Basic Biological Safety; Lab Chemical Safety; and PPE Awareness for Labs. However, the assistant did not complete the online training requirement for work with rDNA, and will be required to complete the rDNA Research - *NIH Guidelines* course.

Laboratory issues uncovered by the investigation:
- Following administration to the animal, the syringe with cannula attachment was not placed directly into a sharps container.
- The surgeons and research assistant were not listed on the approved recombinant DNA registration document.
- The administration of recombinant material into pigs was not listed on the approved rDNA registration document.

Has the IBC reviewed this incident?	YES NO

	If yes, please provide a copy the minutes of the IBC meeting in which the incident was reviewed. October 10 and 24, 2013
Has a root cause for this incident been identified?	YES If yes please describe: Following administration to the animal, the syringe with cannula attachment was not placed directly into a sharps container.
Describe measures taken by the institution to mitigate any problems identified. For measures identified but not yet taken, please include a timeline for their implementation: (use additional space as necessary) The administration procedure will be modified such that following administration to the animal, any needles or cannulas will be placed directly into a sharps container. The BSO met with the PI and reviewed the requirements for rDNA registration, including the registration of all staff involved in rDNA experiments as well as the listing of all animal species that will be exposed to rDNA. The PI will formally request that his approved rDNARD be amended to include the three staff members in question and the injection of the recombinant material into pigs.	

- **Please provide copies of any documents referenced in this report.**
- **Additional information may be requested by OBA after review of this report depending on the nature of the incident.**

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NIH OBA Incident Reporting Template

For reporting Human Gene Transfer Adverse Events a separate template is available at: http://oba.od.nih.gov/oba/rac/Adverse_Event_Template.pdf

Does this incident involve research subject to the *NIH Guidelines*?	YES If no, this incident does not have to be reported to OBA
Institution name:	The University of Iowa
Date of report:	February 17, 2014
Reporter name and position:	Louis V. Kirchhoff, MD, MPH; IBC Chair
Reporter telephone:	319-356-7227
Reporter email:	louis-kirchhoff@uiowa.edu
Reporter mailing address:	Dept of Internal Medicine UIHC – SW54 GH Iowa City, IA 52242
Date of incident:	Unapproved rDNA experiments began September 17, 2013 and were halted on February 3, 2014
Name of principal investigator:	Stanley Perlman, MD, PhD
Is this an NIH funded project?	YES
If yes, please provide:	NIH grant or contract number: A1060699.06A1
	NIH funding institute or center: NIH NIAID
	NIH program officer contact information (name, email etc): Erik Stemmy Email: erik.stemmy@nih.gov
What was the **nature** of incident?	Receiving recombinant MERS-CoV DNA from an outside institution and performing experiments with rMERS-CoV without obtaining prior approval from the IBC. Failure to register a laboratory worker with the IBC prior to his performing rDNA experiments and the failure of that worker to complete the University's rDNA course required for persons working with rDNA.

Did the Institutional Biosafety Committee (IBC) approve this research	NO If yes, on what date?
If yes, please provide:	Approval date:
	Approved biosafety level(s) for the research:
	Additional approval requirements:
What section(s) of the *NIH Guidelines* is the research subject to?	Section III-D-1
Has a report of this incident been made to other federal or local agencies? If so please indicate by checking the appropriate box.	NO
Description of recombinant or synthetic agent or material involved (please indicate strain, attenuation etc. as relevant.)	The construction of rMERS-CoV viral clones expressing GFP and RFP has been completed, and *in vitro* experiments demonstrating the expression of GFP and RFP by the rMERS-CoV clones have been performed. The propagation of these clones for subsequent experiments has not been performed. The construction of a rMERS-CoV viral clone having a point mutation in the ADRP (adenosine diphosphate ribose-1"-monophosphatase) region of the NSP3 (non-structural protein 3) coding sequence has been completed, but no propagation of that clone has been performed.

DESCRIPTION OF INCIDENT: (use additional space as necessary)

Introduction:
On February 3, 2014, the University of Iowa's Biosafety Officer (BSO) became aware that experiments involving rMERS-CoV that had not been reviewed and approved by the IBC were being performed in the laboratory of Dr. Stanley Perlman, a principal investigator (PI) in the Departments of Microbiology and Pediatrics. The BSO contacted the PI, who confirmed that such unapproved work was in fact being performed in his laboratory. The BSO then ordered the PI to immediately halt all experiments involving rMERS-CoV and the PI indicated that he would do so. This incident constitutes a violation of the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (Appendix G-II-B-2-k) and therefore must be reported to the Office of Biotechnology Activities at the National Institutes of Health (NIH/OBA). This report, which follows our initial notification of NIH/OBA on February 3, 2014, provides a description of the investigation of this incident, an analysis of the factors underlying the incident, and the University's planned remedial measures intended to prevent the recurrence of incidents of this type.

Description of incident:

September 14, 2013 The PI received a BAC clone carrying a full-length MERS-CoV cDNA from a collaborator in Spain.

September 17, 2013 Two post-doctoral researchers in the PI's laboratory transformed bacterial cells with the MERS-CoV BAC clone with the goal of making back-up stocks for freezing.

October 22, 2013 The post-doctoral researchers initiated cloning experiments in which genes encoding GFP and RFP were inserted individually into the BAC clone, replacing open reading frames (ORFs) 3 or 5.

November 8, 2013 Construction of rMERS-CoV BAC clones into which GFP or RFP had been inserted and the making of back-up stocks was completed. Up to this point all the work with rMERS-CoV had been done in the PI's laboratory at BSL2 containment and when interviewed in early February by Environmental Health & Safety (EHS) staff the two researchers stated that they had used standard PPE for this work, which included laboratory coats and gloves. In mid-November the work with MERS-CoV BAC GFP and RFP clones was moved to the Carver College of Medicine's BSL3 facility. Some time prior to moving the work with these clones to the BSL3 facility the Oversight Committee for the latter had approved a standard operating procedure (SOP) submitted by the PI entitled "Host-virus interactions in human SARS-CoV extension to MERS-CoV," but this SOP only covers experiments involving non-recombinant MERS-CoV.

December 5, 2013 Construction of a MERS-CoV BAC clone having a point mutation in the ADRP (adenosine diphosphate ribose-1"-monophosphatase) region of the NSP3 (non-structural protein 3) coding sequence was initiated in the PI's laboratory at BSL2 containment. This construct was completed two weeks later.

December 6, 2013 In the BSL3 facility the post-doctoral researchers initiated transfections with the rMERS-CoV BAC clones to produce viral clones carrying the GFP and RFP coding sequences. This work was carried forward to the point at which resulting stocks of the rMERS-CoV viral

clones were titered and expression of the markers was demonstrated.

January 10, 2014 In the BSL3 facility the post-doctoral researchers initiated transfections with the rMERS-CoV BAC clone containing the point mutation in the NSP3 coding sequence. Collections of supernatants from the transfected cells have been collected, but no further experiments have been done with this material.

When interviewed in early February the post-doctoral researchers stated that they had used all standard PPE for such work in the BL3 facility, which includes scrubs, wrap-around gowns, PAPR, double pair of gloves with initial pair taped to cuff of gown, dedicated shoes, socks and shoe covers..

As of the time of the incident, the PI and one of the post-doctoral researchers had completed the required course "rDNA Research-*NIH Guidelines*". The other post-doctoral researcher had not completed this course. Moreover, he had not been listed on any of the PI's approved rDNA Registration Documents as a staff member working with rDNA. All other training required by the University for biological research as well as additional training for BSL3 work, which include Basic Biological Safety; Lab Chemical Safety; PPE Awareness for Labs; and BSL3 Orientation/Refresher training had been completed by the post-doctoral researchers. The latter individuals also had completed the occupational health requirements mandated for all persons working in the BSL3 facility, which include archiving an initial blood sample, respirator evaluation, and an annual clinic visit.

Has the IBC reviewed this incident?	YES If yes, please provide a copy the minutes of the IBC meeting in which the incident was reviewed.
Has a root cause for this incident been identified?	YES This incident was the result of negligence on the part of the PI. He did not obtain IBC approval for the experiments involving the rMERS-CoV performed by the two post-doctoral researchers in his laboratory and in the BSL3 facility. In addition, the PI did not effectively communicate to his post-doctoral researchers the importance of obtaining prior approval from the IBC for experiments involving rDNA and the importance of reviewing relevant SOPs prior to initiation of any experiments in the BSL3 facility. The importance of completing all training requirements prior to the initiation of experimental work also was not effectively communicated. The PI has a long history of obtaining IBC approval for work with rDNA.

Describe measures taken by the institution to mitigate any problems identified. For measures identified but not yet taken, please include a timeline for their implementation: (use additional space as necessary)

To ensure compliance of the PI with the *NIH Guidelines*, we propose setting up an administrative structure under which the PI's rDNA research will be monitored closely during a substantial probationary period. Under this structure, the PI and his subordinate staff members who work with

rDNA will meet on a monthly basis with the BSO, one other EHS staff member involved in the regulation of rDNA work, and one of the virologist members of the IBC. At these meetings the PI and his staff will be asked to present in detail their planned and current rDNA work. The information provided will then be discussed in the light of the PI's approved and pending rDNA Registration Documents (rDNARDs) to ensure appropriate registration of rDNA work. The effectiveness of this monitoring program will be assessed by EHS staff after the initial probationary period and the findings will be presented to the IBC. The members of the latter will then decide to end the monitoring or continue it for an additional probationary period. I welcome your thoughts and suggestions on the structure and duration of this approach for ensuring the PI's compliance with the *NIH Guidelines*.

In addition to the above, the following actions have been taken. On February 10, 2014, the BSO met with the PI and reviewed all his approved rDNARDs. The PI's electronic portal to the latter documents was also reviewed and he was instructed on how to designate laboratory staff as "viewers" so that they can access them.

Following the meeting with the PI, the BSO met with the laboratory staff members assigned to the MERS-CoV and SARS-CoV projects and demonstrated how to access and review the rDNARDs.

Established BSL3 procedures require that all approved BSL3 SOPs must be accessible to persons inside the BSL3 facility. The BSO requested that a binder containing the PI's SOPs be assembled and placed in a common room inside the BSL3 facility. A staff member in the PI's laboratory has been instructed to contact the BSO when copies of all the PI's SOPs have been placed in the binder. All BSL3 users are aware that any experiment carried out in the BSL3 facility must be in an approved SOP, and the PI's staff members have been reminded of the requirement for their review of SOPs prior to initiating new experiments.

- **Please provide copies of any documents referenced in this report. Copies of minutes for the IBC meetings held on February 13 and February 17, 2014, are attached.**
- **Additional information may be requested by OBA after review of this report depending on the nature of the incident.**